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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,072	04/03/2007	Siegfried Ansorge	PMP-0003	6887

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EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	**PAPER NUMBER**
1612	

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05/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,072	ANSORGE ET AL.	
	Examiner	Art Unit	
	CHRIS E. SIMMONS	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8 and 10-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8 and 10-15* is/are rejected.

7)☒ Claim(s) *1-3,5-8 and 10-15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/03/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 02/21/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Objections

Claim 1 is objected to because of the following informalities: The claim seems to be missing words to complete the claim. It is suggested that the claim be amended to read as follows: "A method for the cytoprotective treatment of a chronically obstructive lung disease, comprising…". Appropriate correction is required.

Claims 1-3, 5-8, and 10-15 are objected to because of the following informalities: the term "sibilin" is misspelled in claims 1, 3, 14, and 15. It should be "silibinin". The term "silibilin" is misspelled in claim 12. It should be "silibinin". Appropriate correction is required.

Claim 7 is objected to because of the following informalities: the term wherein" should be added between the terms "claim 1" and "silibinin". The term "is" should be changed to "are". Appropriate correction is required.

Claim 12 is objected to because this currently amended claim has the term "Use" struck-through as if it was present in the prior claim set filed on 08/10/2007. However, the term "use" was not in the prior claim set. On the other hand the term "the" was already in the prior claim set but Applicant has it underscored in the instant claim set as if it is newly added. Claim 12 in the prior claim set read as follows:

> "12. (New) A method for the simultaneous, separate or timed cytoprotective treatment of chronically obstructive lung diseases comprising administering silibinin, its salts and/or its pro-drugs with a-lipoic acid."

Accordingly, the instant claim 12 was not properly amended according to MPEP § 1.121.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter,

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims recite "effectors of glutathione metabolism". There is insufficient written basis in the specification for "effectors of glutathione metabolism" as a genus class because no reasonable correlation between structure and function is provided, other than the disclosure of specific species. There is, however, sufficient written description for the species ambroxol and silibinin and their salts.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made the invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as "effectors of glutathione metabolism" used herein), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ 2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fail to distinguish any steroid from others having the same activity or function. A description of what a material does rather than of what it is, usually does not suffice. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis Added).

A description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Cali. v. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under §112, ¶ 1, by showing the enablement of a representative number of species within a genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that are encompass by the genus. If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not specifically define what constitutes a representative number of species, the courts have indicated what does not constitute same. See, e.g., In re Gostelli, 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989), holding that the disclosure of two chemical compounds within a subgenus did not adequately describe such subgenus.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

In this case, the speciation does not provide a reasonably representative disclosure of useful "effectors of glutathione metabolism" – generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions.

Claim Rejections - 35 USC § 112 - 2nd Pargaraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-11 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The independent claim 1 is limited to silibinin or a salt thereof and α-lipoic acid or a salt thereof; however, the dependent claims 10 and 11 broadens the scope to an effector of glutathione and α-lipoic acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-8, and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keller et al. (USP 6,262,019) in view of Bisgaard et al. ("Drug Delivery to the Lung"; Informa Health Care (2002); page *v.* ISBN:0824705416).

The primary reference discloses a composition comprising sylmarin (i.e., silibinin) and α-lipoic acid used for treating emphysema, a COPD disease (claims 1, 3, 21, and 24). It further discloses in (col. 2, lines 25-31), pulmonary diseases are among the

disease associated with reduced glutathione levels; and in claim 23 it teaches the systemic administration to treat various pulmonary diseases. The preparation may contain additives such as liquid solvents and suspending agents (col. 6. lines 12-14). EXAMPLE 1 discloses a composition comprising 100 to 2500 mg of the lipoic acid and silibinin which can be given once or twice a day (col. 6, line 53 bridging col. 7, line 20). The comprising language of the instant claims allows for the presence of other essential ingredients in the primary reference. The primary reference does not expressly teach inhalation as a possible route of administration.

The secondary reference discloses that aerosol drug delivery allows treatment to be targeted to the lower airways and total systemic exposure to be reduced. It does not expressly teach treating a chronically obstructed lung with a composition comprising silibinin and α-lipoic acid.

The skilled artisan would have found it to be obvious to treat a human with a chronically obstructed lung with a composition comprising silibinin and α-lipoic acid by administering through inhalation being motivated by the desire to administer the composition to the airways while minimizing total systemic exposure.

As for claims 2, 3 and 13-15, it is not patentable to optimize the concentration of ingredients in a composition through routine experimentation. Differences in concentration from what is disclosed in the reference, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. It is not inventive to discover the optimum or workable ranges by routine experimentation. (See MPEP 2144.05 [R-5] II A).

Claims 1-3, 5-8, and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Engelen et al. ("Altered Glutamate Metabolism Is Associated with Reduced Muscle Glutathione Levels in Patients with Emphysema"; Am J Respir Crit Care Med. 2000 Jan;161(1):98- 103.) in view of the combination of Keller et al. (USP 6,262,019) and Bisgaard et al. ("Drug Delivery to the Lung"; Informa Health Care (2002); page *v.* ISBN:0824705416).

The primary reference discloses that emphysema, a COPD, is associated with depleted glutathione (GSH) values in the skeletal muscle (abstract). Since glutathione is an antioxidant, its depletion may lead to chronic oxidative stress and contribute to muscle damage. The reference does not expressly disclose the treatment of COPD using a combination of alpha-lipoic acid and silibinin.

The combination of the secondary and tertiary references and the rationale for their combination is outlined *supra*. The secondary reference does not expressly teach inhalation as a possible route of administration and the tertiary reference does not expressly teach treating a chronically obstructed lung with a composition comprising silibinin and α-lipoic acid.

The skilled artisan, however, would have found it to be obvious at the time of the invention to treat emphysema by administering, through inhalation, a composition comprising α-lipoic acid and silibinin. Said artisan would have been motivated by the desire to decrease oxidative stress in muscle tissue associated with a chronically obstructed lung.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is

(571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Chris E Simmons/
Examiner, Art Unit 1612

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